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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,265	08/31/2001	Timothy A. Springer	CBN-002CP	1985

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/945,265	Applicant(s) SPRINGER ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-31 and 73-75* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 24-31 and 73-75 are pending.

2. Applicant's election with traverse of Group XXVIII, claims 24-31, (now claims 24-31 and 73-75) as they read on an antibody that selectively binds to a modified integrin I-domain in the open conformation filed on 8/27/02, is acknowledged.

Applicant's traversal is on the grounds that a sufficient search and examination with respect to the inventions of Groups XIX-XXVIII can be made with out serious burden on the Examiner since Groups XIX-XXVIII are all directed to antibodies which are specific to a subunit and have exactly the same class and subclass designations. This is not found persuasive because the specific antibodies that specifically binds $\alpha 1$, $\alpha 2$, $\alpha 10$, $\alpha 11$, $\alpha 6$, αD, αE, αL, αX and LFA-1 are recognized divergent subject matter. In addition, the different antibodies are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Therefore the specific antibodies are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claim 24 is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention, because amended claim 24 does not read on elected Group XXVIII. Amended claim 24 now recites a method of using a modified integrin I-domain polypeptide stabilized in the open conformation as an assay reagent to identify an antibody that selectively binds to an integrin I-domain in the open conformation.

4. Claims 25-31 and 73-75 are under examination.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 28 is indefinite in the recitation "a pharmaceutical composition" because it base claim 25 recites an antibody and it is unclear how the antibody would further comprises a pharmaceutical composition.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 25-27, 29-31 and 73-75 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc Natl Acad Sci 98:2393-2398, 2002).

Huang *et al* teach five antibodies BL5, F8.8, May.035, TS1/22 and TS2/6 which selectively bind to an integrin I-domain (see page 3163 under mAbs and Cell Lines, and page 3164 Figure 2 in particular). Those antibodies bind to specific epitope on the integrin αL subunit of I-domain of LFA-1 integrin (page 3164 Figure 2 in particular). Although Huang *et al* do not teach the specific antibodies bind to a modified integrin I-domain in the open conformation, the antibodies bind to an activation specific epitope (I domain) on the integrin, the antibodies blocks an interaction between an integrins and a cognate ligand, wherein said modified I-domain of an αL subunit contains amino acid substitutions K287C/K294C or E284C/E301C and wherein modified LFA-1 I-domain contains amino acid substitutions K287C/K294C or E284C/E301C, all these limitations are considered an inherent property of the reference antibodies.

As is evidenced by Li *et al*, that antibodies against αL I domain of LFA-1, BL5, F8.8, May.035, TS1/22 and TS2/6 bind to the open or "active" mutants K287C/K294C of αL subunit of LFA-1 "modified I domain" (see Table 1 page 2394 in particular). Furthermore, Lu *et al* teach that BL5, F8.8, May.035, TS1/22 and TS2/6 antibodies strongly inhibited binding of both wild-type and mutant K287C/K294C of αL subunit of LFA-1 (page 2395, Table 2 in particular).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to a modified integrin I –domain in the open conformation and binds an activation specific epitope on the integrin I-domain recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 25-27, 29-31 and 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) in view of Owens *et al* (1994).

The teachings of Huang *et al* and Lu *et al* cited as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of an antigen binding fragment.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment, or a $F(ab')_2$ fragment. Owens *et al* further teach antibody fragments are the reagents of choice for some clinical applications (see the entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the antibodies taught by Huang *et al* as Fab and $F(ab')_2$ fragments taught by the Owens *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary

skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claim 28 is rejected under 35 U.S.C. 103(a) as being obvious over Huang *et al* (Proc. Natl. Acad. Sci. 94:3162-3167, 1997), as is evidenced by Lu *et al* (Proc. Natl. Acad. Sci. 98:2393-2398, 2002) in view of U.S Patent No. 6,413,963.

The teachings of Huang *et al* and Lu *et al* cited as an evidentiary reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition and a pharmaceutically acceptable carrier.

The `963 patent teaches pharmaceutical compositions prepared comprise a therapeutically effective amount of a compound (e.g. antibody) in a pharmaceutically acceptable carrier. The `963 patent further teaches that therapy with inhibitors of cell adhesion are indicated for any condition in which an excess of integrin-mediated cell adhesion is a contributing factor (see column 18, lines 28-41 and column 20 lines 11-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the antibodies taught by Huang *et al* reference in a pharmaceutical compositions in a pharmaceutically acceptable carrier taught by the `963 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because antibody pharmaceutical compositions are used in a therapy where any condition in which an excess of integrin-mediated cell adhesion is a contributing factor as taught by `963 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

14. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
October 21, 2002

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